# PATENT COOPERATION TREATY

# PCT

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## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>3113/MNM/r | **FOR FURTHER ACTION** | See Form PCT/IPEA/416 |
|---|---|---|
| International application No.<br>PCT/EP2004/050251 | International filing date *(day/month/year)*<br>04.03.2004 | Priority date *(day/month/year)*<br>18.03.2003 |
| International Patent Classification (IPC) or national classification and IPC<br>A61K31/704 | | |
| Applicant<br>PHARMACIA ITALIA SPA et al. | | |

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

| | | |
|---|---|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☐ | Box No. VIII | Certain observations on the international application |

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 08.10.2004 | 03.05.2005 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Loher, F<br>Telephone No. +49 89 2399-7839 |

# INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/050251

## Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   **Description, Pages**

   1-21 as originally filed

   **Claims, Numbers**

   1-45 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 38-42 (IA)

because:

☒ the said international application, or the said claims Nos. 38-42 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-45 |
| | No: | Claims | |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 1-45 |
| Industrial applicability (IA) | Yes: | Claims | 1-37 and 43-45 |
| | No: | Claims | |

2. Citations and explanations (Rule 70.7):

**see separate sheet**

**Art 33(2)** The subject-matter of claims 1-45 is new in the sense of Article 33(2) PCT, since prior art does not disclose a combination comprising one compound selected from present formulae I-VI and a cycloxygenase-2-inhibitor.

**Art 33(3)** The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1-45 does not involve an inventive step.

D1, which is considered to represent the most relevant state of the art, discloses the combined use of the cyclooxygenase-2 inhibitor B-8 of the present application and several anthracycline antibiotics such as doxorubicin in the treatment of cancer.
The problem to be solved by the present invention may therefore be regarded as how to provide an improved combination suitable for the treatment of cancer comprising an anthracyclin and a cyclooxygenase-2-inhibitor.
On a more abstract level the technical contribution to the state of the art suggested by the present application is a new medical use of known compounds. It must, thus, be of particular relevance that the compounds in question work over the whole range of the claimed use.
D2 teaches that nemorubicin (present compund I) is more effective in the treatment of cancer than doxorubicin. D3 discloses the combined use of present compounds I and II together with other antineoplastic agents in order to achieve synergistic effects. D4, D5 and D6 disclose the efficacy of present compounds I, II, III, V and VI in the treatment of cancer.

Taking into account the teaching of the cited prior art the following reasoning applies:

The applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person. Being aware of the teaching of D1 the skilled man performed an arbitrary choice out of one list containing all anthracyclin antibiotics to select present compounds I-VI to combine them with cyclooxygenase-2 inhibitors. Although not necessary, the teaching of D2 and D3 (nemorubicin being more effective than doxorubicin and the general suggestion to combine anthracyclines with other antineoplastic agents in order to achieve a synergistic effect) directed the skilled man even to choose nemorubicin out of said list.

In letter dated 13.03.2005, the applicant argues, that D1 does not provide any biological data to substantiate the efficacy of a combined treatment using an anthracyclin antibiotic together with a cyclooxygenase-2 inhibitor.

The applicant's attention is drawn to the fact that the same is true for the present application, which does not show any biological data either. Consequently it is held that the teaching of the present application is directly and unambiguously derivable from the teaching of the cited prior art without providing any surprising effect. Therefore, the solution proposed in claims 1-45 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

**Art 33(4)** For the assessment of the present claims 38-42 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject-matter of claims 1-37 and 43-45 is considered to be industrially applicable in the sense of Art 33(4) PCT.